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POSTER ABSTRACTS

503.CLONAL HEMATOPOIESIS, AGING AND INFLAMMATION

Mitochondria-Mediated (MAVS) Innate Immune Signaling Drives Inflammation-Induced Bone Marrow Failure

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Bone marrow failure syndromes (BMFS) are life threatening diseases, characterized by impaired fitness of hematopoietic stem cells (HSC) and ineffective hematopoiesis causing the absence of one or more hematopoietic lineages in the peripheral blood. Substantial clinical data indicate that hyperactivity of inflammatory cytokines, including TNFα, IL-6, and transforming growth factor-β (TGFβ), directly contribute to BMF. Inflammatory challenges result in irreversible HSC functional decline, including decreased repopulation potential and myeloid-bias differentiation. We recently showed that the combination of inflammatory challenges, including polyinosinc:polycytidilic acid (pIC - a double stranded RNA [dsRNA]) plus high TGFβ causes chronic pancytopenia, anemia, expanded hematopoietic stem and progenitor cell pools, and enhanced bone marrow dysplasia, mimicking a myelodysplastic syndrome (MDS) that developed 3-4 months after pIC challenge (Javier et.al. Haematologica 2022). However, the mechanisms behind this association and/or causality are still ill-defined. Here, we show that mitochondrial antiviral signaling (MAVS) protein can mediate the negative effect of pIC and TGFβ on HSC functions and BMF/ MDS development.

Differential gene expression analyses in HSCs suggested that pIC plus TGFβ altered expression of nuclear-encoded mitochondrial genes. Mitochondria serve as platform for the activation of MAVS and downstream innate immune signaling in response to dsRNA. We thus examined the role of mitochondria and MAVS in pIC plus TGFβ-induced BMF/MDS. We show that overexpression TGFβ and pIC together cause alterations in mitochondrial proteins and membrane potential as well as enhanced caspase1 activity, but not the necroptotic signals p-RIP1 and p-RIP3, in HSCs. pIC exposure caused an increase in MAVS expression, and a redistribution into large aggregates that localize onto mitochondria in HSCs, indicative of MAVS activation (two days after pIC exposure in vivo). The MAVS aggregates resolved into smaller and dispersed clusters by 3 months after pIC exposure in control mice. In contrast, in HSCs from TGFβ overexpressing mice, MAVS aggregates persisted 3 months after pIC exposure.

To determine the impact of augmented MAVS in dsRNA+TGFβ-driven BMF, we used MAVS deficient mice crossed with TGFβ overexpressing mice. We found that absence of MAVS protein restored normal white blood cell count, including neutrophils and lymphocytes, restored normal red blood cell but not platelet counts in TGFβ overexpressing mice after pIC challenge, compared to controls. Remarkably, MAVS deficiency partially rescued the dysplastic features of bone marrow myeloid cells in TGFβ overexpressing mice after pIC challenge. MAVS-deficiency also reduced the increased caspase1 activity and lowers mitochondria membrane potential in HSCs of these mice. In serial competitive transplant studies, MAVS-deficiency conferred HSC repopulation advantage. These findings suggest that pIC+TGFβ overexpression mediated BMF/MDS phenotype depends on chronic activation of MAVS.

Because MAVS aggregation depends on mitochondrial fusion, we used genetic loss of the mitochondrial fission regulator Drp1. Drp1-deficiency caused severe mitochondrial aggregation in HSCs; this was associated with sustained MAVS aggregation. In response to pIC, Drp1-deficient mice exhibited increased caspase-1 activity, increased mitochondrial membrane potential and increase in HSC numbers 6 months after pIC challenges. Drp1 loss resulted in anemia and mild pancytopenia. Interestingly, Drp1-deficient bone marrow myeloid progenitors exhibited severe dysplastic features after pIC challenged. These findings suggest that chronic mitochondrial and MAVS aggregation are sufficient to drive BMF/MDS phenotype. Finally, we investigated the levels of epigenetic markers (acetyl H3K27 and methyl H3 Lys4) in HSCs after pIC stress. H4K4me3 levels were decreased in HSCs long-term after pIC challenges [6 months], this was further decreased in Drp1-deficient HSCs. In conclusion, these findings indicate that non-genetic factors contribute to the onset of BMF/MDS. Mitochondria and MAVS protein together mediate an innate immune mechanism that drives BMF/MDS. This study opens the possibility to target mitochondria-related proteins as a therapeutic strategy to restore ineffective hematopoiesis due to chronic inflammation.

Disclosures No relevant conflicts of interest to declare.

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